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Term: CpG with Th2

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L1: Entry 2 of 27 File: PGPB Mar 13, 2003

DOCUMENT-IDENTIFIER: US 20030050261 A1
TITLE: Immunostimulatory nucleic acid molecules

Abstract Paragraph (1):
Nucleic acids containing unmethylated CpG dinucleotides and therapeutic utilities based on their ability to stimulate an immune response and to redirect a Th2 response to a Th1 response in a subject are disclosed. Methods for treating atopic diseases, including atopic dermatitis, are disclosed.

Summary of Invention Paragraph (16):
[0016] The instant invention is based on the finding that certain nucleic acids containing unmethylated cytosine-guanine (CpG) dinucleotides activate lymphocytes in a subject and redirect a subject's immune response from a Th2 to a Th1 (e.g. by inducing monocytic cells and other cells to produce Th1 cytokines, including IL-12, IFN-.gamma. and GM-CSF). Based on this finding, the invention features, in one aspect, novel immunostimulatory nucleic acid compositions.

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L1: Entry 5 of 27 File: PGPB Nov 7, 2002

DOCUMENT-IDENTIFIER: US 20020165178 A1
TITLE: Immunostimulatory nucleic acids for the treatment of anemia, thrombocytopenia, and neutropenia

Summary of Invention Paragraph (14):
[0013] The immunostimulatory effects of CpG-ODN further include the activation of professional antigen-presenting cells in vitro to secrete large amounts of IL-1, IL-3, IL-6, IL-12, GM-CSF, and TNF-.alpha.. On balance, CpG-ODN characteristically skews an immune response strongly toward a Th1-type phenotype and away from a Th2-type phenotype, i.e., toward an immune response dominated by IFN-.gamma. and IL-12. This has been applied to advantage in its use as a T-cell adjuvant and as a treatment for Th2-mediated allergy and asthma.

L1: Entry 6 of 27 File: PGPB Nov 7, 2002

DOCUMENT-IDENTIFIER: US 20020164341 A1
TITLE: Use of nucleic acids containing unmethylated CpG dinucleotide as an adjuvant

Detail Description Paragraph (16):
[0048] Based on the ability of the CpG oligonucleotides to shift the immune response in a subject from a Th2 (which is associated with production of IgE antibodies and allergy) to a Th1 response (which is protective against allergic reactions), an effective dose of a CpG oligonucleotide can be administered to a subject to treat or prevent an allergy.

Detail Description Paragraph (95):
[0125] In other aspects the invention includes a method of inducing a Th1 immune response in a subject by administering to the subject a combination of adjuvants in an effective amount for inducing a Th1 immune response. The combination of adjuvants includes at least one oligonucleotide containing at least one unmethylated CpG dinucleotide and at least one non-nucleic acid adjuvant. It was not previously known that when CpG was combined with a non-nucleic acid adjuvant, as described above, that the combination would produce an immune response with a Th1 profile to an extent that the individual adjuvants could not produce alone. Preferably the extent of the Th profile produced by the combination of adjuvants is synergistic. Another aspect of the invention is to induce a Th response by using CPG with a non-nucleic acid adjuvant that by itself induces a Th2 response.

Detail Description Paragraph (96):
[0126] As described above a Th2 profile is characterized by production of IL-4 and IL-10. Non-nucleic acid adjuvants that induce Th2 or weak Th1 responses include but are not limited to alum, saponins, oil-in-water and other emulsion formulations and SB-As4. Adjuvants that induce Th1 responses include but are not limited to MPL, MDP, ISCOMS, IL-12, IFN-.gamma., and SB-AS2. When the CpG oligonucleotide is administered with a non-nucleic acid adjuvant the combination of adjuvants causes a commitment to a Th1 profile, that neither the adjuvant nor the CpG oligonucleotide is capable of producing on its own. Furthermore, if the non-nucleic acid adjuvant on its own induces a Th2 response, the addition of CpG oligonucleotide can overcome this Th2 bias and induce a Th1 response that may be even more Th1-like than with CpG alone.

Detail Description Paragraph (170):
[0193] Immunization with either HBsAg alone or with alum induces a predominantly Th2-type humoral response with virtually no IgG2a antibodies, which are induced in response to Th1-type cytokines such as IL-12 and IFN-.gamma.. Rather, almost all (>99%) antibodies were of the IgG1 isotype IgG2a:IgG1=0.01. CpG ODN induces significantly more IgG2a antibodies, such that they made up at least 50% of the total IgG (IgG (IgG2a:IgG1=1.4). The combination of alum and CpG ODN induce an equally strong Th1 response as CpG ODN alone (IgG2a:IgG1=1.0), despite the extremely strong Th2-bias of alum (FIG. 5). Similarly CTL responses with CpG ODN plus alum were as strong as those with CpG ODN alone, despite the fact that the Th2-bias of alum resulted in a complete loss of CTL when alum was used alone (FIG. 1).

Detail Description Paragraph (171):
[0194] The strong Th1 bias with CpG is even more evident in neonatal and young mice, which are known to naturally have a strong Th2-bias to their immune system. In this case, neither alum nor CpG ODN on their own induced detectable IgG2a, indicating a very poor or absent Th1 response. Remarkably, when used together, CpG ODN and alum induced high levels of IgG2a antibodies, which were now the predominant form of IgG (FIG. 10). Similarly, neither CpG ODN or alum induced significant levels of CTL in young mice, yet when used together there was a strong CTL response, that was even stronger than

obtained with a DNA vaccine (FIG. 9).

Detail Description Paragraph (172):
[0195] The strength of the Th1 influence of CpG ODN is seen not only by its ability to dominate over the Th2 effect of alum when they are co-administered, but also to induce Th1 responses in animals previously primed for a Th2 response with alum. Immunization with HBsAg using alum as an adjuvant completely abrogates the CTL response owing to the strong Th2 bias of alum (FIGS. 1 and 4). However, in mice using alum at prime and CpG at boost, good CTL were induced, indicating the possibility of CpG to overcome a previously established Th2 response (FIG. 4).

Detail Description Paragraph (173):
[0196] Aluminum hydroxide (alum) is currently the only adjuvant approved for human use. An important disadvantage of alum is that it induces a Th2-rather than a Th1-type immune response, and this may interfere with induction of CTL. Indeed, in mice immunized with recombinant HBsAg, the addition of alum selectively blocked activation of CD8+ CTL (Schirmbeck et al., 1994). Although not essential for protective immunity against HBV, CTL may nevertheless play an important role. For example, a lack of HBV-specific CTL is thought to contribute to the chronic carrier state. In contrast, one of the primary advantages of CpG DNA over alum as an adjuvant is the Th1-bias of the responses and thus the possibility to induce CTL. A striking finding from the present study is that CpG can completely counteract the Th2-bias of alum when the two adjuvants are delivered together, and in the case of immunization in early life, the combination can even give a more Th1 response than CpG ODN alone. This could allow one to capitalize on the strong synergistic action of the two adjuvants on the humoral response while still allowing CTL in adults, and to induce a stronger Th1 response in infants.

Detail Description Paragraph (174):
[0197] The use of alum has been linked to Th2-type diseases. The much higher prevalence of asthma (another Th2-type disease) in more highly developed nations may be linked to the high hygiene level and rapid treatment of childhood infections (Cookson and Moffatt, 1997). Early exposure to bacterial DNA (and immunostimulatory CpG motifs) pushes the immune system away from Th2- and towards a Th1-type response and this may account for the lower incidence of asthma in less developed countries, where there is a much higher frequency of upper respiratory infections during childhood. Addition of CpG ODN as adjuvant to all pediatric vaccines could re-establish a Th1-type response thereby reducing the incidence of asthma.

Detail Description Paragraph (177):
[0198] The synergistic effect of CpG ODN on Th1 responses was also seen using other adjuvants. IFA on its own induces a very strong Th2-type response with virtually no IgG2a antibodies (IgG2a:IgG1=0.002) and CpG ODN on its own induces a moderate Th1 response (IgG2a:IgG1=1.4), but together the response was very strongly Th1 (IgG2a:IgG1=24.0). It is notable that this is even more Th1 than the response induced by CFA (ratio=0.5) (FIG. 6).

CLAIMS:

34. The method of claim 1, wherein the non-nucleic acid adjuvant by itself give a Th2 immune response (e.g. alum) but when used in combination with the CpG oligonucleotide gives a Th1 response.

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L1: Entry 7 of 27 File: PGPB Oct 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020156033
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020156033 A1

TITLE: Immunostimulatory nucleic acids and cancer medicament combination therapy for the treatment of cancer

PUBLICATION-DATE: October 24, 2002

US-CL-CURRENT: 514/44; 424/277.1, 424/85.5, 514/251, 514/449, 514/50, 514/509, 514/8

APPL-NO: 09/ 800266 [PALM]
DATE FILED: March 5, 2001

RELATED-US-APPL-DATA:
Application is a non-provisional-of-provisional application 60/187214, filed March 3, 2000,

RELATED APPLICATIONS

[0001] This application claims priority under Title 35 .sctn.119(e) of the U.S. Provisional Application No. 60/187,214, filed Mar. 3, 2000, and entitled "Immunostimulatory Nucleic Acids and Cancer Medicament Combination Therapy for the Treatment of Cancer", the entire contents of which are incorporated herein by reference.

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L1: Entry 11 of 27 File: PGPB May 30, 2002

DOCUMENT-IDENTIFIER: US 20020064515 A1
TITLE: Methods and products for stimulating the immune system using immunotherapeutic oligonucleotides and cytokines

Detail Description Paragraph (3):
[0037] The finding is based on the discovery that when an immunostimulatory CpG oligonucleotide is administered to a subject in combination with an immunopotentiating cytokine the resultant immune response is synergistic. Both CpG oligonucleotides and immunopotentiating cytokines have the ability to produce immune responses on their own s when administered to a subject. When the combination of the two is administered together, however, the quantity and type of immune response shifts. For instance, when the CpG oligonucleotide and immunopotentiating cytokine are administered in conjunction with an antigen using repeat immunizations, as shown in FIG. 3, a synergistic induction in antigen specific IgG is observed. Additionally, when CpG and GM-CSF are administered together an antibody response develops that includes both IgG2a (indicative of a Th1 immune response) and IgG1 (indicative of a Th2 immune response) whereas when GM-CSF is administered alone IgG2a antibodies are undetectable or low depending on the strain of the animal.

Detail Description Paragraph (28):
[0061] Allergies are generally caused by IgE antibody generation against harmless allergens. The cytokines that are induced by unmethylated CpG oligonucleotides are predominantly of a class called "Th1" which is most marked by a cellular immune response and is associated with IL-12 and IFN-.gamma. and production of IgG2a antibody. The other major type of immune response is termed as Th2 immune response, which is associated with more of an IgG1 antibody immune response and with the production of IL-4, IL-5 and IL-10. In general, it appears that allergic diseases are mediated by Th2 type immune responses and autoimmune diseases by Th1 immune response. Based on the ability of the combination of CpG oligonucleotides and immunopotentiating cytokine to shift the immune response in a subject from a Th2 (which is associated with production of IgE antibodies and allergy and is produced in response to GM-CSF alone) to a Th1 I response (which is protective against allergic reactions), an effective dose of a CpG oligonucleotide and immunopotentiating cytokine can be administered to a subject to treat or prevent an allergy.

Detail Description Paragraph (102):
[0133] Dendritic cells form the link between the innate and the acquired immune system by presenting antigens as well as through their expression of pattern recognition receptors which detect microbial molecules like LPS in their local environment. The combination of immunopotentiating cytokine and CpG oligonucleotide showed induction of Th1 specific antibody when immunopotentiating cytokine alone only produced Th2 specific antibody. Since dendritic cells form the link between the innate and the acquired immune system the ability to activate dendritic cells with CpG and immunopotentiating cytokine supports the use of combination CpG-immunopotentiating cytokine based strategies for immunotherapy against disorders such as cancer and allergic or infectious diseases. The combination of CpG and immunopotentiating cytokine shows synergistic activation of dendritic cells.

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L1: Entry 13 of 27 File: PGPB Nov 22, 2001

PGPUB-DOCUMENT-NUMBER: 20010044416
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010044416 A1

TITLE: Immunostimulatory nucleic acids for inducing a Th2 immune response

PUBLICATION-DATE: November 22, 2001

US-CL-CURRENT: 514/44; 514/110, 514/179, 514/9

APPL-NO: 09/ 768012 [PALM]
DATE FILED: January 22, 2001

RELATED-US-APPL-DATA:
Application is a non-provisional-of-provisional application 60/177461, filed January 20, 2000,

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L1: Entry 16 of 27 File: USPT Aug 6, 2002

DOCUMENT-IDENTIFIER: US 6429199 B1
TITLE: Immunostimulatory nucleic acid molecules for activating dendritic cells

Other Reference Publication (41):
Kline JN et al., Immune redirection by CpG oligonucleotides. Conversion of a Th2 response to a Th1 response in a murine model of asthma. J Invest Med 45(3):282A, 1997.

Other Reference Publication (42):
Kline JN et al., CpG oligonucleotides can reverse as well as prevent Th2-mediated inflammation in a murine model of asthma. J Invest Med 45(7):298A, 1997.

L1: Entry 22 of 27 File: USPT Apr 10, 2001

DOCUMENT-IDENTIFIER: US 6214806 B1
TITLE: Use of nucleic acids containing unmethylated CPC dinucleotide in the treatment of LPS-associated disorders

Brief Summary Text (12):
The present invention is based on the finding that nucleic acids containing at least one unmethylated cytosine-guanine (CpG) dinucleotide affect the immune response in a subject by activating natural killer cells (NK) or redirecting a subject's immune response from a Th2 to a Th1 response by inducing monocytic and other cells to produce Th1 cytokines. These nucleic acids containing at least one unmethylated CpG can be used to treat pulmonary disorders having an immunologic component, such as asthma or environmentally induced airway disease.

Other Reference Publication (39):
Kline JN et al., Immune redirection by CpG oligonucleotides. Conversion of a Th2 response to a Th1 response in a murine model of asthma. J Invest Med 45(3):282A, 1997.

Other Reference Publication (40):
Kline JN et al., CpG oligonucleotides can reverse as well as prevent Th2-mediated inflammation in a murine model of asthma. J Invest Med 45(7):298A, 1997.

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L1: Entry 24 of 27 File: DWPI Nov 22, 2001

DERWENT-ACC-NO: 2002-138610
DERWENT-WEEK: 200227

TITLE: Inducing an antigen specific immune response useful in treating Th1-mediated inflammatory disorders, e.g., (non)-autoimmune diseases or cancer, comprises administering a Th2-immunostimulatory nucleic acid and an antigen

INVENTOR: DAVIS, H L; MCCLUSKIE, M J

PRIORITY-DATA: 2000US-177461P (January 20, 2000), 2001US-0768012 (January 22, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20010044416 A1	November 22, 2001		050	A61K048/00
AU 200131080 A	December 24, 2001		000	A61K039/39
WO 200195935 A1	December 20, 2001	E	000	A61K039/39

INT-CL (IPC): A61 K 9/00; A61 K 31/573; A61 K 31/675; A61 K 31/7088; A61 K 38/13; A61 K 38/19; A61 K 39/00; A61 K 39/002 ; A61 K 39/02; A61 K 39/08; A61 K 39/12; A61 K 39/145; A61 K 39/29; A61 K 39/295; A61 K 39/39; A61 K 39/395; A61 K 48/00; A61 P 3/10; A61 P 17/06; A61 P 31/00; A61 P 31/04; A61 P 33/00; A61 P 35/00; A61 P 37/00; A61 K 39/00; A61 K 38:19

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L1: Entry 27 of 27 File: DWPI Sep 3, 1998

DERWENT-ACC-NO: 1998-480941
DERWENT-WEEK: 199841

TITLE: Use of nucleic acids containing an unmethylated CpG - for treating a subject having or at risk of having an acute decrement in air flow or inhibiting an inflammatory response

INVENTOR: KRIEG, A M; SCHWARTZ, D A

PRIORITY-DATA: 1997US-039405P (February 28, 1997), 1998US-0030701 (February 25, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9837919 A1	September 3, 1998	E	065	A61K049/00
AU 9866674 A	September 18, 1998		000	A61K049/00
EP 1039935 A1	October 4, 2000	E	000	A61K049/00
US 6214806 B1	April 10, 2001		000	A61K031/70
AU 738513 B	September 20, 2001		000	A61K049/00
JP 2001513776 W	September 4, 2001		061	A61K031/7084

INT-CL (IPC): A01 N 43/04; A61 K 31/70; A61 K 31/7084; A61 K 31/7088; A61 K 49/00; A61 P 11/00; C07 H 21/02; C07 H 21/04 ; C12 N 15/09